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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,501	04/22/2002	Hiroyuki Saito	053466-0325	9449

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,501	SAITO ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/29/2007 has been entered.

Claims 45-56 are pending and under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **These rejections are maintained for reasons made of record in the Office Actions dated 4/18/2006, 12/27/2006, and for reasons set forth below.**

Claim 45 (from which all other claims depend) recites a method for "suppressing the growth of blood vessel tissues in a patient in need thereof." Thus, the claimed subject matter has been broadened to include treatment of angiogenesis and neovascularization, in addition to

stenosis and restenosis. New claims 55 and 56 recite antibodies that bind to the same site of human TF as the site bound by the i-b2 antibody. Applicants fail to point out where in the specification support for the new claims can be found. The specification provides an Example wherein pre-treatment with the i-b2 monoclonal antibody suppressed growth of the blood vessel lumen (i.e. intima) in response to physical injury. While this is a single example of treatment of restenosis, it does not provide support for angiogenesis or neovascularization. It only provides support for preventing narrowing of the lumen, not a general inhibition of blood vessel growth, such general inhibition being only a speculation. There is nothing in this passage, or the remainder of the specification, to lead one of skill in the art to use the i-b2 antibody (or any other anti-TF antibody) to suppress blood vessel growth associated with any disease other than restenosis. Furthermore, the specification does not provide support for other antibodies that might bind to the same epitope as i-b2, particularly in light of the fact that the epitope recognized by i-b2 is not disclosed. Therefore, there is no support for the broadened scope of the claims, or the new claims. Thus, the amended claims include impermissible New Matter.

Applicants claim methods for "suppressing the growth of blood vessel tissues in a patient in need thereof" by administration of an antibody having "Factor X binding inhibitory activity" to human tissue factor (human TF). Applicants disclose a single example and TF-specific antibody, i-b2, used in a method of suppressing the growth of the vascular lumen in response to injury. Other TF-specific antibodies did not suppress vascular lumen growth, although they did bind TF. The claims read on a broad genus of methods and human TF antibodies to suppress the growth of blood vessel tissues.

The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention.

Applicant is referred to the guidelines for the Written Description Requirement published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. conserved motifs or domains).

In the instant case the specification fails to disclose a representative number of species by structure and function encompassed by the genus as claimed, i.e. all that is disclosed is that a single TF-specific antibody, i-b2, can bind to human TF and prevent restenosis in an animal model.

The genus as claimed encompasses structurally and functionally distinct members other than the disclosed species. Claiming all divergent species that achieve a result as contemplated

by the application without defining the representative number of species by structure and function is not in compliance with the written description requirement. *Rather, it is an attempt to preempt the future before it has arrived.* "The written description requirement has several policy objectives. The essential goal of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention as claimed is "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention (see Fed. Reg., Vol. 66, No. 4, pp. 1099-11, January 5, 2001).

Since the specification fails to disclose a representative number of species defined by structure and function, it is not possible to envision the claimed composition. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). Therefore, the lack of disclosure in the specification is not deemed sufficient to reasonably convey to one

skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore, possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

In the instant case, the antibodies to be used in the methods as claimed have been defined only by a statement of function that broadly encompasses using any and all TF-specific antibodies that might suppress blood vessel growth and any and all TF-specific antibodies that might prevent binding to Factor X, which conveys no distinguishing information about the identity of the claimed material, such as its relevant structural or physical characteristics.

Furthermore, applicants only disclose a single antibody, i-b2, capable of suppressing the growth of lumenal blood vessel tissues. Neither applicants nor the prior art disclose other human TF antibodies capable of suppressing the growth of blood vessel lumen as claimed, or any TF-specific antibodies capable of suppressing angiogenesis or neovascularization. Neither the instant specification or the prior art disclose antibodies with the claimed "Factor X binding inhibitory" activity to human TF. This is because human TF does not bind Factor X. Human TF binds Factors VII and VIIa, then the complex of TF/Factor VII enzymatically activates Factor X (see page 46, line 21 to page 47, line 2 of the instant specification, and references cited in enablement rejection below). The remainder of the instant disclosure is directed to the inhibition

of blood clot formation (e.g. thrombosis) rather than the inhibition of lumenal blood vessel tissue. Therefore, applicants claim the human TF antibodies for suppression of the growth of blood vessel tissues, and antibodies that inhibit Factor X binding by function only, without a correlation between structure and function. The diversity of the possible human TF antibodies involved coupled with the lack of disclosure regarding human TF antibodies capable of inhibiting the binding of Factor X to TF, would require the skilled artisan to conclude that the single example presented by the applicants is not sufficient to describe the claimed genus.

Claims 45-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the i-b2 antibody to suppress restenosis, does not reasonably provide enablement for using other TF-specific antibodies to suppress any other types of blood vessel growth, e.g. angiogenesis or neovascularization. Furthermore, the specification does not provide enablement for any TF-specific antibodies that inhibit the binding of Factor X to human TF, or antibodies that bind to the same epitope on human TF as i-b2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The claims broadly recite a method of inhibiting blood vessel growth by administration of TF-specific antibodies. Types of blood vessel growth include stenosis, restenosis, angiogenesis, and neovascularization. The instant specification discloses the use of one human TF-specific monoclonal antibody (i-b2) to suppress restenosis, and does not mention the use of human TF antibodies to suppress blood vessel growth related to angiogenesis or neovascularization.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics,* Inc. 8 USPQD2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is a conclusion reached by weighing several factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art and State of the art. The art concerning inhibition of blood vessel tissue growth by administration of human TF antibodies is unpredictable. There is no mention of the administration of such antibodies to patients in need of angiogenesis inhibition (e.g. cancer patients) in the prior art, or in applicants' disclosure. In a review of angiogenesis inhibitors published in 2004 (five years after applicants filing date), Eskens (British J. Cancer, 2004, of record) teaches antibodies specific for VEGF or VEGFR as angiogenesis inhibitors, but there is no mention of human TF antibodies as inhibitors of angiogenesis. Thus, the effects of administering human TF antibodies to a patient in need of suppression of angiogenesis or neovascularization are unknown, and therefore unpredictable. In a review of monoclonal antibody therapy of cancer (angiogenesis and neovascularization are requirements for tumor growth), Weiner (Sem. Oncol., 1999) teaches that antibodies are larger than most chemotherapy agents, and thus have slower distribution kinetics than small molecules, and thus limited tissue penetration. There also exist physiological barriers to antibody penetration of tumors, and it is thus predicated that the therapy of large tumors with antibodies will be compromised. The human immune response to monoclonal antibodies that contain murine sequences is also a problem. See page 43, first column, first full ¶ to page 44, first column. In a review of the types

of monoclonal antibodies used in cancer therapy as of 1999, Weiner et al fail to mention any that target human TF (pages 44-47). The instant disclosure fails to address any of the issues raised by Weiner et al regarding the *in vivo* use of monoclonal antibodies to treat cancer.

Regarding the claimed activity of the antibodies in inhibiting the binding of Factor X to human TF, these molecules do not bind each other. Ragni et al (Circulat., 1996, of record) and Carmeliet et al (Int. J. Biochem. Cell Biol., 1998, of record) both teach that TF complexes with factors VII and VIIa, which permits enzymatic activation of Factor X by the proteolytic activity of Factor VIIa. See page 1913, second column, first full ¶ of Ragni et al and page 661, second column and legend of Fig. 1 of Carmeliet et al. There is absolutely no support in the prior art that Factor X binds human TF, thus, applicants are claiming antibodies that inhibit an activity that does not exist.

The state of the art regarding the inhibition of blood vessel tissue growth by administration of human TF antibodies is thus poorly developed, as is the art of producing antibodies that inhibit the Factor X binding activity of human TF. The development of efficacious human TF antibodies with the claimed activity would have to be done empirically, along with the development of the appropriate methods (e.g. dosage, delivery).

Number of working examples. Applicants have provided a working example of inhibiting restenosis with the i-b2 TF-specific antibody. Applicants have provided no working examples of TF-specific antibodies that suppress any other types of blood vessel tissue growth (e.g. angiogenesis), nor methods of administering such antibodies, nor TF-specific antibodies that inhibit the binding of Factor X to human TF.

Amount of guidance. Other than restenosis, applicants provide no direction or guidance for the claimed methods of inhibiting other types of blood vessel tissue growth by administration of TF-specific antibodies, or guidance for producing TF-specific antibodies that inhibit the binding of Factor X. The specification requires the skilled artisan to practice trial and error experimentation in order to produce and characterize different TF antibodies, dosage limitations, and administration methods to determine which (if any) will be efficacious as claimed, or inhibit Factor X binding as claimed.

Scope of the invention. The claims are broad in nature and read on the administration of any TF-specific antibody to a patient in need of suppression of blood vessel tissue growth, regardless of the type of blood vessel tissue involved (e.g. the claims read on a method to treat most, if not all, cancers).

Nature of the invention. The invention involves the unpredictable art of treating blood vessel tissue growth with TF-specific antibodies that inhibit the binding of Factor X.

Level of skill in the art. While the level of skill in the art of treating hypercoagulation-related diseases with TF-specific antibodies is high, the level of skill in the art of suppressing blood vessel tissue growth with such antibodies is low. The unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and

excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Response to Arguments

Applicant's arguments filed 5/29/2007 have been fully considered but they are not persuasive. Applicants essentially assert that the claim amendments overcome the Written Description rejection. This is not persuasive for reasons set forth above in the Written Description rejection.

Regarding the enablement rejection, applicants essentially assert that: 1) tissue factor is involved in stenosis, restenosis, angiogenesis, and neovascularization, thus, the inhibition of tissue factor could reasonably be expected to suppress the growth of blood vessels; 2) because the claimed antibody is useful for the inhibition of the growth of blood vessels, it is clear that the claimed antibody is useful for treatment of angiogenesis and neovascularization; 3) the i-b2 antibody binds to human TF, which binds Factor X, thus it is clear that human TF is important for the inhibition of the growth of blood vessels; and, 4) once the i-b2 antibody has been obtained, it would be routine to obtain others like it.

Regarding 1), 2) and 4), there is no evidence to support these assertions, rather, it appears merely binding to TF does not equate with the claimed functionality, as demonstrated by applicants: the b-b and i-b antibodies bind TF, but did not inhibit restenosis. Therefore, in order to make and use an antibody according to the instant claims that suppresses angiogenesis, it is not merely a matter of preparing anti-TF antibodies. The role of TF in tumor biology is completely independent from its role in coagulation/restenosis (i.e. to bind Factors VII and VIIa and initiate the blood coagulation cascade). This is supported by Zhang et al (cited by

applicants, Exhibit A), who teach (last sentence of the abstract and page 1326, ¶ bridging first and second columns) that the role of TF in angiogenesis and tumor biology is due to an increase in growth regulatory molecules, a mechanism distinct from its activation of coagulation, as discussed above (i.e. it binds and activates Factors VII and VIIa to initiate the coagulation cascade). Thus, it is easy to envision that whereas certain anti-TF antibodies may inhibit coagulation or restenosis, the same antibodies do not necessarily inhibit blood vessel growth in general. Regarding 3), this statement, on its face, is untrue. To reiterate, human TF does not bind Factor X. See the references cited above in the enablement rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 51 recites the limitation "the constant region" in line 5. There is insufficient antecedent basis for this limitation in the claim.

Claim 55 recites the limitation "the same site as a site of the human TF" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633